IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LIMITED Defendants.	:	Civil Action No. 04-171-KAJ **REDACTED VERSION**

PLAINTIFF GLAXO GROUP LIMITED'S
OPENING CLAIM CONSTRUCTION BRIEF CONSTRUING
THE DISPUTED CLAIM TERMS OF GLAXO'S U.S. PATENT NO. 5,068,249

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I. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiff Glaxo Group Limited ("Glaxo") patented a new and improved aqueous oral syrup formulation of ranitidine, an anti-ulcer medicine sold under the brand name Zantac® Syrup. On or about February 5, 2004, Glaxo received notice that defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Limited ("defendant" or "Teva") submitted Abbreviated New Drug Application No. or generic Ranitidine Oral Solution USP, 15mg/mL (Teva's "ANDA Product") to the Food and Drug Administration ("FDA"). Defendant certified to the FDA that its ANDA Product would not infringe Glaxo's U.S. Patent No. 5,068,249 (the " '249 patent") and requested FDA approval prior to the patent's expiration date. Glaxo filed its complaint in this action on March 18, 2004 alleging infringement of the claims (1-12) of the '249 patent. The '249 patent expires on November 26, 2008.

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During the course of discovery, defendant Teva admitted that its ANDA Product contains all of the claim elements of claims 1-12 of Glaxo's '249 patent except for four claim elements that are the subject of this brief. Discovery closed on May 26, 2006[1] with expert depositions concluding on June 8, 2006. The issue of claim construction is ripe for consideration by the Court. Pursuant to Paragraph 12 of the Scheduling Order, Glaxo submits this opening brief and the accompanying Declarations of Oren D. Langer[2] and Bradley D. Anderson[3] in support of its proposed construction of the disputed claim language.

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1 Except for a recent dispute between the parties concerning a document only recently identified by Teva on its privilege log and then subsequently produced upon request by counsel for Glaxo.

2 "Langer Decl." refers to the "Declaration of Oren D. Langer, in Support of Plaintiff Glaxo Group Limited's Opening Claim Construction Brief and Summary Judgment Motions on U.S. Patent No. 5,068,249" submitted herewith.

3 "Anderson Decl." refers to "Declaration of Bradley D. Anderson, Ph.D. in Support of Plaintiff Glaxo Group Limited's Opening Claim Construction Brief on U.S. Patent No. 5,068,249" submitted herewith.

II. SUMMARY OF ARGUMENT

Ranitidine is the active ingredient in Glaxo's patented Zantac® Syrup, an anti-ulcer medicine. Glaxo enjoys market exclusivity for this product until November 26, 2008 because of the protection afforded by the '249 patent. The United States Patent and Trademark Office ("PTO") granted the '249 patent because a Glaxo researcher, Dr. David Long, unexpectedly discovered the benefit of adding ethanol to an aqueous formulation of ranitidine for oral administration in order to enhance the stability of ranitidine and prolong the shelf-life of the drug product. This unexpected discovery of enhanced ranitidine stability, imparted by adding ethanol to an aqueous formulation of ranitidine for oral administration, is supported by Glaxo's extensive stability studies on Zantac® Syrup formulations with and without ethanol.

Claim 1 of the '249 patent reads:

> A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine, and/or one or more of its physiologically acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5-7.5.

(Langer Decl. Ex. 1, Col. 2:67-Col. 3:4). The specification of the '249 patent describes how Dr. Long "surprisingly found that the *stability of ranitidine* in aqueous based formulations and more particularly aqueous based formulations for oral administration *may be substantially enhanced* by the addition of ethanol to the formulation." (*Id.* at Col. 1:40-44) (emphasis added). The specification goes on to explain that "[t]he *amount* of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*." (*Id.* at Col. 1:54-56) (emphasis added). The invention of the '249 patent, therefore, is centered on using a stabilizer, ethanol, to enhance the stability of ranitidine in an aqueous formulation for oral administration.

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The claim construction proposed by Glaxo is consistent with the intrinsic evidence of the '249 patent, prosecution history and cited prior art references, and it is in accordance with Federal Circuit law:

- [Claims 1-12] The claim language "a stabilizing effective amount of" should be construed to mean: "An amount sufficient to enhance the stability of the ranitidine active ingredient in an aqueous formulation for oral administration;"
- [Claims 1-12] The claim language "ethanol" should be construed to mean: "An organic compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07;"
- [Claim 2] The claim language "2.5% to 10% weight/volume ethanol" should be construed to mean: "2.5% to 10% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient in the aqueous formulation for oral administration;"
- [Claims 3, 11 and 12] The claim language "7% to 8% weight/volume ethanol" should be construed to mean: "7% to 8% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient in the aqueous formulation for oral administration;" and
- [Claims 1-10] The claim language "aqueous formulation for oral administration" should be construed to mean: "A water based formulation, wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount),

administered orally for gastrointestinal absorption." [Claims 11-12] Similarly, the claim language "aqueous formulation of ranitidine suitable for oral administration" should be construed to mean: "A water based formulation of ranitidine, wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption."

Glaxo's proposed claim construction also is consistent with the plain and ordinary meaning of the claim language to one of ordinary skill in the art. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). Glaxo respectfully requests that the Court adopt Glaxo's proposed claim construction for the reasons set forth below.

III. STATEMENT OF FACTS

A. Technical Background Relevant To Glaxo's Patented Invention

Several factors are typically considered when formulating a drug product, including the route of administration, safety and efficacy, solubility, physical stability, chemical stability and excipient capabilities. (Anderson Opening Rpt.[4] ¶ 18). Various types of drug dosage forms exist, such as tablets, capsules, oral solutions (*e.g.*, syrups) and injectable or intravenous forms. (*Id.* at ¶ 19). At issue here are aqueous formulations of ranitidine (or one of ranitidine's physiologically acceptable salts) suitable for oral administration. Ranitidine is the active ingredient in Glaxo's patented Zantac® Syrup formulation.

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[4] "Anderson Opening Rpt." refers to "Bradley D. Anderson, Ph.D., Fed. R. Civ. P. 26(a)(2) Expert Witness Report Concerning The Issue of Infringement of Glaxo's '249 Patent" attached as Exhibit A to the Anderson Decl.

The active ingredient in all drug products will degrade over time. (Anderson Opening Rpt. ¶ 20; REDACTED . An active ingredient of a drug product can break down or degrade in different ways, commonly including hydrolysis or oxidation reactions.[6] (Anderson Opening Rpt. ¶ 24; Kibbe Dep. at 18:9 – 20:8, Langer Decl., Ex. 24). These chemical reactions cause susceptible chemical bonds in the active ingredient to break, leading to the formation of new molecules or substances that are referred to as degradants or impurities. (*Id.*). The goal when formulating a drug product is to enhance chemical stability by inhibiting or slowing down the degradation of the active ingredient such that the drug product has a shelf-life long enough for it to be produced, distributed, stored and used for a commercially viable period of time after manufacture. (Anderson Opening Rpt. ¶ 20;

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The chemical stability of the active ingredient in a drug product is determined largely from the results of stability studies that measure the rate of degradation of the active ingredient in the drug product under certain specified conditions. (Anderson Opening Rpt. ¶ 20; Kibbe Dep. at 42:7 - 43:11, Langer Decl., Ex. 24). In general, the higher the temperature the more rapidly

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[6] Hydrolysis reactions occur in the presence of water, and oxidation reactions occur in the presence of oxygen. (Anderson Opening Rpt. ¶ 24; Kibbe Dep. at 18:9 - 20:8, 43:16-21, Langer Decl., Ex. 24).

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the active ingredient in an aqueous formulation for oral administration will degrade. (Anderson Opening Rpt. ¶ 21).

It is standard practice to test the chemical stability of an active ingredient by subjecting it to temperatures above room temperature (25°C). (*Id.*). This is called "accelerated" stability testing because it artificially forces the active ingredient to degrade or break down much more rapidly than it would under normal room temperature (25°C). (*Id.*). Stability studies may also be carried out at room temperature (25°C) or lower, but such studies require more time, because the active ingredient breaks down more slowly as compared to accelerated conditions. (*Id.*). An applicant seeking FDA marketing approval of a drug product typically performs stability testing of the drug product under both accelerated testing conditions of 40°C and 75% relative humidity and room temperature conditions of 25°C and 60% relative humidity. (*Id.* at ¶ 22).

The shelf-life of a drug product is determined, in-part, by the time during which a drug product will, if properly stored, retain an acceptable amount of the active ingredient in the selected dosage form. (Anderson Opening Rpt. ¶ 20; **REDACTED**

There are scientifically accepted equations that allow scientists to analyze stability study data and to predict shelf-life at room temperature. (Anderson Opening Rpt. ¶¶ 22, 43 and 44). A measure of the stability of an active ingredient, such as ranitidine in an aqueous formulation for oral administration, is the "t_{95} value." (*Id.* at ¶ 44). The t_{95} value is time (t) required for the amount of ranitidine in the aqueous formulation at room temperature to degrade to 95% of its initial concentration at the time of formulation. (*Id.*). The FDA requires an applicant to perform stability testing of its proposed drug product, and the FDA provides standard industry guidance requiring that calculations of shelf-life from stability study data be based on the lower 95% confidence limits of the t_{95} value rather than the t_{95} value itself. (*See* 21

C.F.R. § 211.166, Langer Decl., Ex. 20; FDA Guidance at G0035954-959, Langer Decl., Ex. 18; Anderson Opening Rpt. ¶ 22). The lower 95% confidence limit of t_{95} is the most conservative statistical treatment for calculating expected shelf-life from stability study data.

It is important to be conservative in the calculation of shelf-life because one wants to be sure that patients receive the label claim dosage of the active ingredient without receiving unnecessary amounts of degradation impurities. '249 File History at G000176, G00143, Langer Decl., Ex. 10).

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B. The '249 Patented Invention

1. Glaxo's Development Of The Original Zantac® Syrup Formulation Without Ethanol As A Stabilizer

In or about July 1976, Glaxo's scientists discovered and synthesized ranitidine. Ranitidine, the active ingredient in Zantac® Syrup, controls gastric acid by selectively blocking the "H_2" (Histamine 2) receptor site on special cells (called "parietal cells") lining the stomach. This H_2 receptor site – when triggered with histamine – provokes a release of gastric acid into the stomach for digesting food, but excess stomach acid can cause ulcers and acid reflux. By selectively blocking the H_2 receptor site, Zantac® Syrup blocks histamine and prevents the release of gastric acid, thereby preventing and healing gastric ulcers and relieving acid reflux.

From the late 1970s to early 1980s, scientists in Glaxo's Pharmaceutical Research group experimented with different pharmaceutical formulations of ranitidine, including an aqueous formulation for oral administration.[8] *See Glaxo Wellcome, Inc. v. Pharmadyne Corp.*, 32 F.

[8] An aqueous oral solution or syrup formulation is particularly useful for young children, the elderly and anyone else in need of an anti-ulcer medicine who has trouble swallowing solid dosage forms (*i.e.*, tablets or capsules) of the drug.

Supp. 2d 265, 277 (D. Md. 1998). (*See also* Long Tr.[2] 277-79, Langer Decl. Ex. 3). In November 1983, Glaxo submitted a Notice of Claimed Investigational Exemption for a New Drug ("IND") for Zantac® Syrup to the FDA. *See id.* (*See also* Glaxo IND at G007121, Langer Decl. Ex. 4). The original formulation for Zantac® Syrup, outlined in the IND, contained ranitidine hydrochloride and various excipients, including an antimicrobial preservative system to protect the syrup against bacterial contamination. *See id.* (*See also* Glaxo IND at G007138, Langer Decl. Ex. 4). The original Zantac® Syrup formulation did not contain ethanol, but it demonstrated adequate chemical stability of ranitidine and also protected the syrup against the microorganisms listed in the United States Pharmacopeia ("USP"). *See id.* (*See also* Glaxo IND at G007138, G007193, Langer Decl. Ex. 4). After submission of the IND, further work in Glaxo's Pharmaceutical Research Laboratories revealed that, although the formulation was preserved against the microorganisms listed in the USP, the original formulation supported the growth of a waterborne bacterium known as *Pseudomonas cepacia*. *See id.* (*See also* Glaxo NDA at G006164, Langer Decl. Ex. 5; Long Tr. 279-81, Langer Decl., Ex. 3).

In or about July 1985, an in-use test on Glaxo's original non-ethanol formulation for Zantac® Syrup revealed a significant loss of one component of the preservative system due to *Pseudomonas cepacia* bacterial contamination. *See Pharmadyne*, 32 F. Supp. 2d at 277. (*See also* Glaxo NDA at G006164, Langer Decl. Ex. 5; Long Tr. 280-81, Langer Decl., Ex. 3; Long 7/25/85 Memo at G026878, Langer Decl. Ex. 6). This contamination problem caused Glaxo to delay its product launch, which came to a "screeching halt." *See id.* (*See also* Long Tr. 279-80, Langer Decl., Ex. 3; Long 7/25/85 Memo at G026878, Langer Decl. Ex. 6). Dr. Long, Glaxo's Pharmaceutical Research Leader and the inventor of the '249 patent invention, had management

[2] "Long Tr." refers to the trial testimony of Dr. David R. Long in the *Pharmadyne* case.

responsibility during 1985 for development of Glaxo's Zantac® Syrup. (Long Tr. 265, 281-82, Langer Decl., Ex. 3).

2. Dr. David Long's Surprising Discovery That Adding Ethanol To An Aqueous Formulation Of Ranitidine For Oral Administration Enhances Ranitidine Stability

Dr. Long devised a strategy for overcoming the bacterial contamination problem in the original formulation for Zantac® Syrup, which ultimately led to his surprising discovery that adding ethanol to an aqueous formulation of ranitidine for oral administration enhances ranitidine stability. *See Pharmadyne*, 32 F. Supp. 2d at 278. (*See also* Long Tr. 281-84, 404-12, Langer Decl. Ex. 3). His strategy called for an assessment of various syrup formulations and challenging those formulations with *Pseudomonas cepacia*. *See id.* (*See also* Long Tr. 284, 404-12, Langer Decl., Ex. 3; Long Notes at G026881-82, Langer Decl., Ex. 7). In or about August 1985, Dr. Long decided to assess a syrup formulation with 5% (weight/volume "(w/v)") ethanol because ethanol was a known and effective antimicrobial preservative for aqueous pharmaceutical products. *See id.* (*See also* Long Tr. 410-12, 417-18, Langer Decl. Ex. 3; Long Notes at G026881-82, Langer Decl., Ex. 7; Lab Notebook P590 at G026729, G026742, Langer Decl., Ex. 8). Dr. Long hoped that the addition of ethanol would cure the bacterial contamination problem without negatively affecting the chemical stability of ranitidine in the formulation. *See id.* at 279. (*See also* Long Tr. 287, 425, Langer Decl., Ex. 3). Based on the results of testing performed at Dr. Long's direction, Dr. Long preliminarily concluded that the 5% (w/v) ethanol formulation solved the problem of *Pseudomonas cepacia* contamination. *See id.* (*See also* Long Tr. 411-12, 417-18, Langer Decl., Ex. 3; Long 8/28/85 Letter at G026879, Langer Decl., Ex. 9; Lab Notebook P590 at G026742, Langer Decl., Ex. 8).

In or about October 1985, Dr. Long and his team concluded that 7.5% (w/v) ethanol would be included in the Zantac® Syrup formulation to ensure that a minimum of 5% (w/v) ethanol would remain in the product formulation throughout its assigned shelf-life to preserve it against *Pseudomonas cepacia* contamination. *See Pharmadyne*, 32 F. Supp. 2d at 278. (*See also* Long Tr. 421-22, Langer Decl., Ex. 3; Lab Notebook P590 at G026807, Langer Decl., Ex. 8). The 7.5% (w/v) ethanol formulation for Zantac® Syrup was put on stability review to determine whether the ranitidine in the new formulation was, in fact, chemically stable throughout the assigned 18-month shelf-life for Zantac® Syrup. *See id.* (*See also* Long Tr. 421-22, Langer Decl., Ex. 3; Lab Notebook P590 at G026865-71, Langer Decl., Ex. 8). Later on, after Glaxo had obtained stability study data for the reformulated Zantac® Syrup containing 7.5% ethanol, analysis of the stability study data surprisingly and unexpectedly indicated that ethanol actually *enhanced* the chemical stability of ranitidine in Zantac® Syrup. *See id.* at 277, 279. (*See also* Long Tr. 424-25, Langer Decl., Ex. 3; Lab Notebook P590 at G026871-73, Langer Decl., Ex. 8). Based on this surprising and unexpected discovery, Glaxo filed British Patent Application No. GB 8629781 on December 12, 1986 in the name of Dr. Long. *See id.* at 279. (*See also* '249 File History at G000249-57, Langer Decl., Ex. 10).

On December 11, 1987, Glaxo filed a corresponding patent application in the United States. *See Pharmadyne*, 32 F. Supp. 2d at 279. (*See also* '249 File History at G000249-57, Langer Decl., Ex. 10). Glaxo claimed foreign priority based on its earlier-filed British Patent Application No. GB 8629781. *See id.* (*See also* '249 File History at G000249-57, Langer Decl., Ex. 10). Glaxo thereafter filed two continuation applications, which led to the issuance of the '249 patent on November 26, 1991.

C. The Specification And Claims Of The '249 Patent

1. The '249 Patent Specification

The '249 patent is entitled "Aqueous Ranitidine Compositions Stabilized with Ethanol." (Langer Decl., Ex. 1, cover page). The '249 patent was issued by the United States Patent and Trademark Office ("PTO") on November 26, 1991 from U.S. Application No. 494,804. (*Id.*).[10] The invention of the '249 patent "relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine." (*Id.* at Col. 1:9-11). The '249 patent first describes Glaxo's own prior art patents disclosing aqueous ranitidine solutions (injection solutions and oral solutions) where shelf-life was improved by adjusting the pH from a pH of 5 to a pH within the range of 6.5-7.5. (*Id.* at Col. 1:12-38).

The '249 patent then characterizes the invention as follows:

> We have now surprisingly found that the *stability of ranitidine* in aqueous based formulations and more particularly aqueous based formulations for oral administration *may be substantially enhanced* by the addition of ethanol to the formulation.
>
> Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.
>
> The amount of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and

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[10] U.S. Application No. 494,804 was filed on March 14, 1990 and is a file wrapper continuation of U.S. Application No. 344,620. (Langer Decl., Ex. 1, cover page). U.S. Application No. 344,620 was filed on April 28, 1989 and is a continuation of U.S. Application No. 131,442, which was filed on December 11, 1987. (*Id.*).

> more particularly is between 5 to 10% w/v, more especially 7-8% w/v."

(Langer Decl., Ex. 1, Col. 1:40-60; *see also* Col. 2:30-34) (italics added). The '249 patent further describes an embodiment of the invention:

> A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.
>
> * * *
>
> The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity enhancing agent.

(*Id.* at Col. 2:2-10 and 38-43).

The '249 patent specification concludes with an "illustrative example" of a formulation according to the invention. This illustrative example includes 1.68% (w/v) ranitidine hydrochloride as the active ingredient, 7.5% (w/v) of the stabilizing agent ethanol, orthophosphate buffers to control pH, a viscosity enhancing agent (hydroxy propylmethylcellulose), antimicrobial preservative, sweetening agents, flavour, and water to 100 ml:

Ranitidine oral liquid formulation (150 mg/10ml) expressed as free base	
	% w/v
Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate	

anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
Sweetening agents	qs
Flavour	qs
Purified water BP to	100ml

(*Id.* at Col. 2:47-65).

2. The '249 Patent Claims

Glaxo's '249 patent contains twelve (12) claims, two of which are independent claims. Independent claims 1 and 11 each contain claim language that is at issue (italicized):

> 1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiological acceptable salts thereof, said formulation comprising *a stabilizing effective amount of ethanol* and said composition having a pH in the range of 6.5 to 7.5.
>
> 11. A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as a free base, said formulation having a pH in the range of 7.0 to 7.3 and also containing *7% to 8% weight/volume ethanol* based on the complete formulation.

(Langer Decl., Ex. 1, Col. 2:67-Col. 3:4 and Col. 4:11-16). Representative claims 2 and 3 of the '249 patent are dependent on claim 1 and also contain claim language that is at issue (italicized):

> 2. A pharmaceutical composition according to claim 1 containing *2.5% to 10% weight/volume ethanol* based on the complete formulation.
>
> 3. A pharmaceutical composition according to claim 1 containing *7% to 8% weight/volume ethanol* based on the complete formulation.

(*Id.* at Col. 3:5-10).

3. Chemistry References Reflecting The Understanding Of One Of Ordinary Skill In The Art

"Ethanol" is the ranitidine stabilizing agent specified and claimed in the '249 patent. Ethanol is an organic compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07. (*See* CRC Handbook of Chemistry and Physics, C-296 (59th ed. 1978), Anderson Opening Rpt. ¶ 72 and Ex. 8). A lower aliphatic hydrocabon group is a straight or branched chain saturated molecule (*i.e.*, carbon-carbon single bonds only) that contain about 1-4 carbon atoms and associated hydrogen atoms. (*See* Morrison, R. and Boyd, R., Organic Chemistry, 200, 573 (4th Ed. 1983), Anderson Opening Rpt. ¶ 77 and Ex. 9). An -OH group is a hydroxyl group occurring on at least one carbon atom in an organic alcohol. (*Id.*).

A "stabilizer" is a "substance that tends to keep a compound, mixture or solution from changing its form or chemical nature." (Hawley's Condensed Chemical Dictionary, 1086 (11th ed. 1987), Anderson Opening Rpt. ¶ 34 and Ex. 5). One of ordinary skill in the art[11] would have understood from reading the '249 patent that the function of ethanol is to enhance the stability of ranitidine in an aqueous formulation for oral administration. (Anderson Opening Rpt. ¶¶ 26, 34). The way in which the function of enhancing ranitidine stability is accomplished, is by adding ethanol to inhibit or slow down ranitidine degradation. (*Id.* and ¶¶ 72-75). The result is

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[11] A person of ordinary skill in the art, at the time of the December 12, 1986 foreign priority date for the '249 patent, would have possessed a B.S. in Chemistry or Pharmaceutical Science and 2-3 years of experience in the formulation and development of pharmaceutical liquid dosage forms. (Bradley D. Anderson, Ph.D., Fed. R. Civ. P. 26(a)(2) Rebuttal Expert Witness Report ("Anderson Rebuttal Rpt.") ¶ 13, attached as Exhibit B to the Anderson Declaration). Alternatively, such a person of ordinary skill could have possessed a Ph.D. in Chemistry or Pharmaceutical Science without any industry experience. (*Id.*).

enhanced shelf-life of the pharmaceutical composition, which is an aqueous formulation for oral administration containing an effective amount of ranitidine. (*Id.*).

D. The Prosecution History Of The '249 Patent

The '249 patent has a foreign application priority date of December 12, 1986, based on British Patent Application No. GB 8629781. (Langer Decl., Ex. 1, cover page). U.S. Application No. 131,442 was filed on December 11, 1987, within one year of the foreign application priority date. (*Id.*). U.S. Application No. 131,442 was later abandoned and a continuation application, U.S. Application No. 344,620, was filed on April 28, 1989. (*Id.*). U.S. Application No. 344,620 was later abandoned and a file wrapper continuation application, U.S. Application No. 494,804, was filed on March 14, 1990. (*Id.*). U.S. Application No. 494,804 issued as the '249 patent on November 26, 1991. (*Id.*).

1. U.S. Application No. 131,442, Filed On December 11, 1987, And Continuation Application No. 344,620, Filed On April 27, 1989

The examination of U.S. Application No. 131,442 and Continuation Application No. 344,620 are substantively quite similar and will be treated together for convenience. Both applications contained the same fourteen (14) original claims. ('249 File History at G000243-44, G000120-21, Langer Decl., Ex. 10). Independent claim 1 was originally filed as follows:

> 1. A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiological acceptable salts thereof, said formulation also containing ethanol.

(*Id.* at G000243, G000120).

In Office Actions dated May 5, 1988 and June 28, 1989, U.S. Patent Office Examiner Friedman rejected claim 1 and other claims of the applications as indefinite and non-enabled under 35 U.S.C. § 112 and as being unpatentable under 35 U.S.C. § 103 over two Chemical Abstracts cited by the Examiner. (*Id.* at G000264-65, G000131-33). Examiner Friedman stated

that the claims were not enabled under 35 U.S.C. § 112 because "[a]ll claims should recite amounts for all ingredients." (*Id.* at G000264, G000131). As to the Examiner's rejection under 35 U.S.C. § 103, he stated that the two Chemical Abstracts taught "the cojoined use of use of [sic] ranitidine and an alcohol (ethanol)." (*Id.* at G000132; *see also* G000265).

Applicant filed responsive Amendments on November 7, 1988 and October 30, 1989, respectively. Applicant amended Claim 1 as follows:

> 1. (Amended) A pharmaceutical composition which is an aqueous formulation <u>for oral administration</u> of ranitidine and/or one or more physiological acceptable salts thereof, said formulation also containing <u>a stabilizing effective amount of</u> ethanol <u>and said composition having a pH in the range of 6.5 to 7.5</u>.

(10/30/89 Amendment, '249 File History at G000139, Langer Decl., Ex. 10; *see also* G000267). Applicant explained to the Examiner that "the amount of ethanol present has been functionally defined. . . . The expression 'also containing ethanol' has been modified to specify that the amount of ethanol contained in the composition is a stabilizing amount of ethanol and this amendment is fully supported by applicant's specification at page 2, lines 4 and 5 ['249 patent, Col. 1:54-56]." (*Id.* at G000267-68, G000140). As to the two Chemical Abstracts cited by the Examiner, applicant explained that "there is no teaching whatever that the stability of ranitidine or its salts as an aqueous formulation for oral administration is enhanced by the presence of ethanol and no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed." (*Id.* at G000142; *see also* G000269).

Applicant further emphasized the importance of stabilizing the active ingredient in a pharmaceutical formulation for oral administration:

> Applicant wishes to reiterate that the stability of a pharmaceutical formulation for oral administration is the most important factor and enhancing the stability of the active ingredient of such formulations is always an objective. Thus, in the

> development of any pharmaceutical formulation, it is necessary to ensure that the drug substance is stable within the formulation and this is necessary for two reasons. Firstly, the drug substance must be stable in order to ensure that the patient is receiving the correct dosage of the drug. Secondly, it is important to ensure that the patient is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This second point is particularly important since it is not always possible to identify fully all of the breakdown products that may occur. Consequently, the chronic toxicity of all the various compounds arising from the breakdown of the drug substance cannot be determined.
>
> In practice, degradation of the drug substance within a formulation usually occurs upon storage and is often dependent upon a number of factors including temperature and time of storage. Any improvement that can be made in enhancing the stability of the drug substance can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, enhancement of the stability of the drug substances also benefit from the economic point of view in that it increases the effective shelf life of the product.

(10/30/89 Amendment, '249 File History at G000143-44, Langer Decl. Ex. 10). On November 29, 1988 and on November 14, 1989, respectively, Examiner Friedman issued Office Actions maintaining the rejections under 35 U.S.C. § 112, questioning the use of the word "also" in claim 1 and indicating that the amount of ranitidine was still not adequately defined. (*Id.* at G000272, G000161). The Examiner also maintained his rejection of the claims over the two Chemical Abstracts under 35 U.S.C. § 103. (*Id.*). The Examiner further stated that "[a]s for the allegation of *enhanced stability*, it has not been demonstrated for the compositions urged as contrasted with any of other pH parameters." (*Id.* at G000161) (italics added).

2. File Wrapper Continuation Application No. 494,804 Filed On March 14, 1990

On March 14, 1990, applicant filed file wrapper continuation application no. 494,804. ('249 File History at G000164, Langer Decl., Ex. 10). The file wrapper continuation application incorporated the amendments that had been made during prosecution of U.S. Application

No. 344,620. In an Office Action dated May 4, 1990, Examiner Friedman repeated his earlier rejections under 35 U.S.C. § 112 and § 103. (*Id.* at G000170-71).

In an Amendment filed on October 31, 1990, claim 1 was further amended as follows:

> 1. A pharmaceutical composition which is an aqueous formulation for oral administration [of][12] an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation ~~also containing~~ comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.

(*Id.* at G000173, G000139). This became the final form of claim 1 in the later-issued '249 patent. Applicant explained that "Claim 1 has been amended to indicate that the ranitidine present is present in an effective amount and to delete the objected to terminology 'also containing'." (*Id.* at G000174). As to the two Chemical Abstracts cited by the Examiner, applicant again explained that: "[T]here is no teaching whatever that the stability of ranitidine or its salts as an aqueous formulation for oral administration is enhanced by the presence of ethanol and no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed." (*Id.* at G000175). Using language nearly identical to that used in the October 30, 1989 Amendment (quoted above at pp. 16-17), applicant reiterated the importance of stabilizing ranitidine in a pharmaceutical formulation for oral administration, explaining, *inter alia*:

> "[E]nhancing the stability of the active ingredients of such formulations [for oral administration] is always an objective. . . . Any improvement that can be made in enhancing the stability of the drug substance can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, enhancement of the stability of the drug substance also

[12] The word "of" was later added by an Examiner's Amendment dated May 30, 1991 in conjunction with the Examiner's June 3, 1991 Notice of Allowability. ('249 File History at G000212-13, Langer Decl. Ex. 10).

> benefits from the economic point of view in that it increases the effective shelf life of the product. There is not even the most remote suggestion of this in the prior art of record."

('249 File History at G000176, Langer Decl., Ex. 10). Applicant also stated that: "Applicant is in the process of preparing a Declaration to substantiate *the unexpected effect of ethanol in enhancing the stability of ranitidine in aqueous oral formulations*." (*Id.* at G000177) (italics added).

On January 22, 1991, new Examiners Waddell and Gardner issued an Office Action stating that: "[R]ejections presented by Examiner Friedman in the Office Action dated 5/4/90 are deemed to be overcome by the amendment filed on 10/31/90." (*Id.* at G000199). The Examiners went on to explain: "However, new rejections must now be presented as a result of the additional documents which were filed on 1/10/91." (*Id.*). Curiously, the Examiners rejected the claims "under 35 U.S.C. § 102(a) and (b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Padfield et al. (GB 2142820)" (*id.* at G000200), a prior art reference that Glaxo had described in the background portion of the '249 patent application and which had been disclosed by Glaxo to the Patent Office at the very beginning of the prosecution. (*See* April 8, 1988 Information Disclosure Statement, '249 File History at G000258-61, Langer Dec. Ex. 10). The Examiners stated:

> Padfield et al. [the '820 patent] teach the *enhanced stability of aqueous compositions of ranitidine* formulated at a pH in the range of 6.5 to 7.5. The applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the rage [sic range] of 6.5 to 7.5 and with the addition of ethanol. It has not been demonstrated in the record, by means of experimental data, that the applicant's invention produces any unexpected results. The disclosure, as presented, is insufficient to overcome the prior art without the aid of experimental data to show a definite improvement over the GB patent [the '820 patent]. Since the GB patent [the '820 patent] teaches an aqueous composition of ranitidine, it is considered well within the state of the art to choose

> ethanol as an additive which would be considered pharmaceutically acceptable when formulating this composition. Absent evidence to the contrary, the addition of ethanol is considered merely to be a choice among known conventional excipients.

(*Id.* at G000200) (italics added).

On May 10, 1991, applicant filed a Request for Reconsideration and enclosed a Declaration of Dr. John Hempenstall (the "Hempenstall Declaration"). (*Id.* at G000204-211). Applicant explained that the Hempenstall Declaration:

> [P]rovides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 [the '820 patent] in terms of the stability of the ranitidine in the composition. In this connection, it is noted that the liquid formulation without ethanol which is used in the Declaration for purposes of comparison is the same as the formulation of Example 3 of Padfield et al. [the '820 patent]. Accordingly, the Declaration presents a direct comparison between a composition according to the present invention and a composition according to the prior art . . . Applicant acknowledges that ethanol has previously been used in pharmaceutical compositions. However, the purpose for which ethanol has been included has been either as a solvent or as a preservative against bacterial contamination. There was, however, no reason to suppose that either of these functions of ethanol would have had any beneficial effects in terms of limiting the degradation of ranitidine in aqueous formulations thereof.

(*Id.* at G000205).

In the Hempenstall Declaration, Dr. Hempenstall explained:

> In the development of any pharmaceutical presentation it is necessary to ensure that the drug substance is stable within the formulation for as long a time period as is practical, so that the patient is receiving the correct dosage and also that he or she is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This latter point is particularly important since it is not always possible to fully identify all the breakdown products that can occur and consequently one cannot determine the chronic toxicity of all the various compounds arising from the breakdown of the drug substance.

('249 File History at G000208-09 ¶ 4, Langer Decl., Ex. 10). Dr. Hempenstall went on to explain: "In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and surprising enhancement in the stability of ranitidine is achieved by the addition of ethanol to the formulation." (*Id.* at G000209, ¶ 5). Stability studies were analyzed by Dr. Hempenstall comparing (i) aqueous ranitidine formulations for oral administration containing 7.5% ethanol in the formulation, to (ii) aqueous ranitidine formulations for oral administration without ethanol in the formulation. (*Id.* at G000209, ¶ 6).

Dr. Hempenstall explained that: "[T]he acceptable shelf life for an aqueous formulation containing ranitidine hydrochloride is considered to be the time at which no more than 5% of the ranitidine present in the formulation has degraded. Accordingly, the figure determined from the stability studies was the time (in months) for 5% ranitidine loss calculated as the lower 95% confidence limit." (*Id.* at G000210, ¶ 6). Dr. Hempenstall concluded that "the formulation with ethanol has an average shelf life at 30°C of 19 months compared with 13 months when ethanol is excluded from the formulation. This is a highly significant and valuable improvement." ('249 File History at G000211, ¶ 6, Langer Decl., Ex. 10). Dr. Hempenstall further concluded that "ethanol has a beneficial effect upon the stability of ranitidine in aqueous based formulations and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect." (*Id.* at G000211, ¶ 7).

Supervisory Patent Examiner Waddell issued a Notice of Allowability on June 3, 1991 in response to the May 10, 1991 Request for Reconsideration and the Hempenstall Declaration. (*Id.* at G000212). The final language of claim 1, approved by the Examiners, and showing the amendments made during prosecution, reads as follows (underline denotes additions and strike-through denotes deletions):

> 1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation ~~also containing~~ comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.

(*Id.* at G000213).

IV. ARGUMENT

A. Claim Construction Principles

Claim construction is a matter of law for the court to decide. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*). The Federal Circuit has stated that the objective of claim construction is to give claim terms " 'their ordinary and customary meaning,' " which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation . . . Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313.

To ascertain the ordinary and customary meaning of a claim term, "the court looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.' Those sources included 'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the

art.'" *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." *Id.* Additionally, "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.' " *Id.* at 1315 (quoting *Vitronics*, 90 F.3d at 1582). Ultimately, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Id.* at 1316 (citing *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

In construing claim terms, a court should consult the patent's prosecution history so that the court can exclude any interpretation that was disclaimed during prosecution. *See id.* at 1317. "Disclaimers based on disavowing actions or statements during prosecution, however, must be both clear and unmistakable." *Sorensen v. ITC*, 427 F.3d 1375, 1378-79 (Fed. Cir. 2005). "Moreover, 'it is the applicant, not the examiner, who must give up or disclaim subject matter that would otherwise fall within the scope of the claims.' " *Id.* at 1379 (quoting *Innova*, 381 F.3d at 1124).

B. Construction Of Terms

1. Claims 1-12: "a stabilizing effective amount of"

Glaxo's Proposed Construction: An amount sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.

Glaxo's proposed construction of "a stabilizing effective amount of" is directly supported by the language of the claims, the specification and the prosecution history of the '249 patent. The '249 patent has two independent claims, claims 1 and 11. While only claim 1 contains the language "a stabilizing effective amount of," added by amendment to define the amount of ethanol in functional terms, Glaxo recognizes the case law that consistency of claim

interpretation requires that this critical claim limitation also applies to the amount of ethanol defined in claim 11. *See Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1356 (Fed. Cir. 2004) ("[S]ubject matter surrendered via claim amendments during prosecution is also relinquished for other claims containing the same limitation. This court follows this rule to ensure consistent interpretation of the same claim terms in the same patent.") (citing *Builders Concrete, Inc. v. Bremerton Concrete Prods. Co.*, 757 F.2d 255, 260 (Fed. Cir. 1985)). Claim 1 of the '249 patent provides:

> 1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiological acceptable salts thereof, said formulation comprising *a stabilizing effective amount of* ethanol and said composition having a pH in the range of 6.5 to 7.5.

(Langer Decl., Ex. 1, Col. 2:67-Col. 3:4) (emphasis added).[13] This functional language describes the amount of ethanol required to stabilize ranitidine effectively in an aqueous formulation for oral administration. (Anderson Dep.[14] at 11:6 - 14:16, 51:7 - 52:15, 66:12-23, 69:20-25, Langer Decl., Ex. 37). In other words, "a stabilizing effective amount of" is the amount of stabilizer sufficient to enhance the stability of the ranitidine active ingredient in an aqueous formulation for oral administration.

The specification of the '249 patent directly supports Glaxo's proposed construction. The specification of the '249 patent explains that "the *stability of ranitidine* in aqueous based formulations and more particularly aqueous based formulations for oral administration *may be substantially enhanced* by the addition of ethanol to the formulation." (Langer Decl., Ex. 1, Col.

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[13] Claim 11 reads: "A pharmaceutical composition . . . also containing 7% to 8% weight/volume ethanol based on the complete formulation." (Langer Decl. Ex. 1, Col. 4:10-16).

1:40-44) (emphasis added). The specification goes on to explain that "[t]he *amount* of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*." (*Id.* at Col. 1:54-56) (emphasis added). From these descriptions in the specification, it is clear that "a stabilizing effective amount of" is the amount sufficient to enhance the stability of the ranitidine active ingredient in an aqueous formulation for oral administration.

One of ordinary skill in the art would understand the description in the '249 patent to mean that the function of ethanol is to enhance the stability of ranitidine by inhibiting or slowing down the degradation of ranitidine in an aqueous formulation for oral administration. (Anderson Opening Rpt. ¶¶ 26, 33, 34 and 75). REDACTED The result of adding ethanol to the formulation is enhanced shelf-life of the pharmaceutical composition containing an effective amount of ranitidine. (Anderson Opening Rpt. ¶ 75). One of ordinary skill in the art would also understand that the enhanced stability of ranitidine in an aqueous formulation for oral administration can be readily assessed in comparison to an aqueous ranitidine formulation for oral administration without ethanol or other equivalent stabilizer. (*Id.* at ¶ 35; Anderson Rebuttal Rpt.[15] ¶¶ 26-27). This does not compel a claim construction incorporating detailed measurement criteria of the type offered by defendant.

The prosecution history of the '249 patent underscores the consistency of the claim construction proposed by Glaxo. During prosecution of the applications that led to the '249 patent, the Examiner rejected claim 1 and other claims as obvious in view of the prior art

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[14] "Anderson Dep." refers to the deposition testimony of Glaxo expert witness Bradley Anderson, Ph.D., taken in this matter on June 8, 2006.

Chemical Abstracts. The Examiner asserted that the prior art taught the "cojoined . . . use of use of [*sic*] ranitidine and an alcohol (ethanol)." ('249 File History at G000132, Langer Decl. Ex. 10; *see also* G000265). In response to the Examiner's rejections, applicant repeatedly explained that in the prior art references cited by the Examiner "there is no teaching whatever that the *stability of ranitidine* or its salts as an aqueous formulation for oral administration *is enhanced by the presence of ethanol* and no suggestion that ethanol should be included in pharmaceutical formulations containing ranitidine as presently claimed." (*Id.* at G000142; *see also* G000269) (emphasis added). Applicant also acknowledged that ethanol previously had been used in pharmaceutical compositions as a solvent or as a preservative against bacterial contamination, but that there was "no reason to suppose that either of these functions of ethanol would have had any *beneficial effects* in terms of *limiting the degradation of ranitidine* and aqueous formulations thereof." (*Id.* at G000205) (emphasis added).

During prosecution of the applications that led to the '249 patent, the Examiner also rejected claim 1 and other claims as being non-enabled because the claims failed to recite "amounts" for all ingredients. ('249 File History at G000264, G000131, G000170, Langer Decl., Ex. 10). In response to the Examiner's rejection, applicant amended the claims to define the amount of ethanol and ranitidine in functional terms (underline denotes additions and strike-through denotes deletions):

> 1. A pharmaceutical composition which is an aqueous formulation <u>for oral administration</u> <u>*an effective amount*</u> of ranitidine and/or one or more physiological acceptable salts thereof, said formulation also ~~containing~~ <u>comprising</u> <u>*a stabilizing*</u>

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[15] As noted above in footnote 11, "Anderson Rebuttal Rpt." refers to "Bradley D. Anderson, Ph.D., Fed. R. Civ. P. 26(a)(2) Rebuttal Expert Witness Report" attached as Exhibit B to the Anderson Decl.

> *effective amount of* ethanol and said composition having a pH in the range of 6.5 to 7.5.

(*Id.* at G000139, G000173; *see also* G000267) (emphasis added). Applicant explained that "the *amount* of ethanol present has been *functionally defined*. . . . The expression 'also containing ethanol' has been modified to specify that the *amount* of ethanol contained in the composition is a *stabilizing amount* of ethanol and this amendment is fully supported by applicant's specification at page 2, lines 4 and 5 ['249 patent, Col. 1:54-56, referencing 'the enhanced stability']." (*Id.* at G000267-68, G000140) (emphasis added). Applicant continued:

> [T]he *stability* of a pharmaceutical formulation for oral administration is the *most important factor* and *enhancing the stability of the active ingredient* of such formulations is always an objective. Thus, in the development of any pharmaceutical formulation, it is necessary to ensure that the *drug substance is stable* within the formulation and this is necessary for two reasons. Firstly, the *drug substance must be stable* in order to ensure that the patient is receiving the correct dosage of the drug. Secondly, it is important to ensure that the patient is not receiving significant amounts of breakdown products arising from the *degradation of the drug substance* in the formulation. This second point is particularly important since it is not always possible to identify fully all of the breakdown products that may occur. Consequently, the chronic toxicity of all the various compounds arising from the *breakdown of the drug substance* cannot be determined.
>
> In practice, *degradation of the drug substance* within a formulation usually occurs upon storage and is often dependent upon a number of factors including temperature and time of storage. *Any improvement* that can be made in *enhancing the stability of the drug substance* can only benefit the patient since it ensures more accurate dosage and the intake of less breakdown products. In addition, *enhancement of the stability of the drug substances* also benefit from the economic point of view in that it increases the effective shelf life of the product.

(*Id.* at G000143) (emphasis added).

The Hempenstall Declaration also "provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-

2142820 [the '820 patent] in terms of the *stability of the ranitidine* in the composition." ('249 File History at G000205, Langer Decl., Ex. 10) (emphasis added). Dr. Hempenstall stated that: "In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and *surprising enhancement in the stability of ranitidine* is achieved by the addition of ethanol to the formulation." (*Id.* at G000209, ¶ 5) (emphasis added). Dr. Hempenstall concluded that "ethanol has a *beneficial effect* upon the *stability of ranitidine* in aqueous based formulations . . . ." (*Id.* at G000211, ¶ 7) (emphasis added).

These explanations support the plain and ordinary meaning of the contested claim language and illustrate what one of ordinary skill in the art would understand from reading the '249 patent and prosecution history. The amount of ethanol required in the formulation is an amount sufficient to enhance the stability of ranitidine in the aqueous formulation for oral administration. In sum, the '249 patent specification and prosecution history compel a construction of the claim language "a stabilizing effective amount of" as "an amount sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration." Glaxo respectfully requests that the Court adopt this proposed claim construction.

2. Claims 1-12: "ethanol"

Glaxo's Proposed Construction: An organic compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07.

There seems to be no real dispute by defendant of Glaxo's proposed construction of "ethanol." The proposed construction is the plain and ordinary meaning of the word as understood by one of ordinary skill in the art of pharmaceutical formulation and development.

(Anderson Opening Rpt. ¶¶ 72, 77 and Exs. 8 and 9; Anderson Rebuttal Rpt. ¶ 13). Claim 1 of the '294 patent provides:

> 1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiological acceptable salts thereof, said formulation comprising a stabilizing effective amount of *ethanol* and said composition having a pH in the range of 6.5 to 7.5.

(Langer Decl., Ex. 1, Col. 2:67-3:4) (emphasis added). Ethanol is a well-known organic alcohol[16] compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07. (*See* CRC Handbook of Chemistry and Physics, C-296 (59th ed. 1978), Anderson Opening Rpt. ¶¶ 72, 77 and Exs. 8, 9)

REDACTED

A lower aliphatic hydrocarbon group is a straight or branched chain saturated molecule (*i.e.*, carbon-carbon single bonds only) that contains about 1-4 carbon atoms and associated hydrogen atoms. (Anderson Opening Rpt. ¶ 77). An -OH group is a hydroxyl group occurring on at least one carbon atom, indicative of an organic alcohol. (*See* Morrison, R. and Boyd, R., Organic Chemistry, 200, 573 (4th ed. 1983), Anderson Opening Rpt. ¶ 77 and Ex. 9).

The '249 patent specification uses the plain and ordinary meaning of the word "ethanol" as understood by pharmaceutical formulation chemists:

> We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of *ethanol* to the formulation.

REDACTED

> Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing *ethanol*. The aqueous formulation is prepared *using ingredients of a purity* such that it is suitable for administration to patients and will in general contain at least one conventional pharmaceutical excipients in addition to the *ethanol* and ranitidine and/or physiologically acceptable salts thereof.
>
> The amount of *ethanol* present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of *ethanol* in the composition on a weight/volume basis of the complete formulation, is within the range of 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v."

(Langer Decl., Ex. 1, Col. 1:40-60). Accordingly, the claim language "ethanol" should be construed to mean: "An organic compound comprising a lower aliphatic hydrocarbon group having two carbon atoms and one -OH group with the chemical formula CH_3-CH_2-OH (or C_2H_5OH) and a molecular weight of 46.07." Glaxo respectfully requests that the Court adopt this proposed claim construction.

3. Claim 2: "2.5% to 10% weight/volume ethanol"

<u>Glaxo's Proposed Construction</u>: 2.5% to 10% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.

Glaxo's proposed construction of "2.5% to 10% weight/volume ethanol" is supported by the claim language, the specification and the prosecution history of the '249 patent. Claim 2 of the '249 patent is dependent on claim 1 and provides:

> 2. A pharmaceutical composition according to claim 1 containing *2.5% to 10% weight/volume ethanol* based on the complete formulation.

(Langer Decl., Ex. 1, Col. 3:5-7) (emphasis added). The dependency of claim 2 on claim 1 is important in view of the discussion above concerning the claim language "a stabilizing effective amount of ethanol" in claim 1. The claim language "2.5% to 10% weight volume ethanol"

further defines the amount of ethanol in claim 1 as a numeric range having a stabilizing effect on ranitidine in an aqueous formulation for oral administration. This is the only construction consistent with the '249 patent specification and prosecution history where applicant emphasized the distinguishing function of adding ethanol to enhance the stability of ranitidine. This construction is also consistent with the legal doctrine that dependent claims incorporate all of the limitations of the independent claim from which they depend. *See* 35 U.S.C. § 112 para. 4; *In re Beaver*, 893 F.2d 329, 330 (Fed. Cir. 1989).

The specification and prosecution history of the '249 patent provide additional specific support for Glaxo's proposed claim construction. In particular, the specification explains that:

> [T]he amount of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range *2.5% to 10%* . . . .

(Langer Decl., Ex. 1, Col. 1:54-56) (emphasis added). The Hempenstall Declaration submitted to the Patent Office discloses the results of stability testing using 2.5% to 10% ethanol in aqueous formulations of ranitidine for oral administration to demonstrate the "beneficial effect" of ethanol on ranitidine stability. ('249 File History at G000211 ¶¶ 6-7, Langer Decl., Ex. 10). Accordingly, the claim language "2.5% to 10% weight volume ethanol" should be construed to mean: "2.5% to 10% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration." Glaxo respectfully requests that the Court adopt this proposed claim construction.

4. Claims 3 and 11: "7% to 8% weight/volume ethanol"

Glaxo's Proposed Construction: 7% to 8% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration.

As with claim 2, the dependency of claim 3 on claim 1 is important to the proper claim interpretation. Claim 3 defines the amount of ethanol in claim 1 as a more limited numerical range having a stabilizing effect on ranitidine in an aqueous formulation for oral administration. Claim 3 depends from claim 1, while claim 11 is an independent claim:

> 3. A pharmaceutical composition according to claim 1 containing *7% to 8% weight/volume ethanol* based on the complete formulation.
>
> 11. A pharmaceutical composition which is an aqueous formulation of ranitidine for oral administration containing 150 mg ranitidine per 10 ml dose expressed as a free base, said formulation having a pH in the range of 7.0 to 7.3 and also containing *7% to 8% weight/volume ethanol* based on the complete formulation.

(Langer Decl., Ex. 1, Col. 3:8-10, Col. 4:10-16). The legal doctrine that dependent claims incorporate all of the limitations of the independent claim from which they depend also applies to claim 3. *See* 35 U.S.C. § 112 para. 4; *Beaver*, 893 F.2d at 330. With respect to claim 11, the amount of ethanol defined in the numerical range of 7% to 8% weight/volume must be sufficient to enhance the stability of "150 mg ranitidine per 10 ml dose expressed as a free base" contained in the "aqueous formulation of ranitidine for oral administration," in accordance with the doctrine of consistent claim construction. *See Impax,* 356 F.3d at 1356 ("[S]ubject matter surrendered via claim amendments during prosecution is also relinquished for other claims containing the same limitation. This court follows this rule to ensure consistent interpretation of the same claim terms in the same patent.") (citing *Builders Concrete*, 757 F.2d at 260).

Glaxo's proposed construction is consistent with the specification and the prosecution history of the '249 patent. (*See supra* Section IV.B.3). The specification explains that:

> [T]he amount of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, *more especially 7-8% w/v*.

(Langer Decl., Ex. 1, Col. 1:54-56) (emphasis added). As in claim 2, the claim language "7% to 8% weight volume ethanol" in claims 3 and 11 should be construed to mean: "7% to 8% weight volume ethanol sufficient to enhance the stability of the ranitidine active ingredient contained in an aqueous formulation for oral administration." Glaxo respectfully requests that the Court adopt this proposed claim construction.

5. Claims 1-10: "aqueous formulation for oral administration," and Claims 11-12: "aqueous formulation of ranitidine suitable for oral administration"

Glaxo's Proposed Construction: A water based formulation [of ranitidine], wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption.

The phrase, "aqueous formulation for oral administration" is used in claim 1 of the '249 patent, which provides:

> 1. A pharmaceutical composition which is an *aqueous formulation for oral administration* of an effective amount of ranitidine and/or one or more physiological acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5 to 7.5.

(Langer Decl., Ex. 1, Col. 2:67-3:4) (emphasis added). The phrase "aqueous formulation of ranitidine suitable for oral administration" is used in claim 11 of the '249 patent, which provides:

> 11. A pharmaceutical composition which is an *aqueous formulation of ranitidine suitable for oral administration* containing 150 mg ranitidine per 10 ml dose expressed as a free base, said formulation having a pH in the range of 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

(*Id.* at Col. 4:10-16) (emphasis added). As with the "ethanol" claim element, defendant does not dispute Glaxo's proposed construction for the quoted claim elements in claims 1 and 11. Teva also has admitted that its accused product satisfies both of the claim elements for purposes of satisfying Glaxo's burden of proof on patent infringement. (6/30/05 Court Conf., D.I. 57 at p. 5). In the absence of a dispute, Glaxo respectfully requests that the Court adopt Glaxo's proposed construction.

V. CONCLUSION

Glaxo's proposed construction of the disputed claim language in the '249 patent is consistent with the plain and ordinary meaning of the words as understood by a person of ordinary skill in the art. Glaxo's proposed construction is also supported by the intrinsic evidence of record. Glaxo respectfully requests that the Court adopt Glaxo's proposed claim construction of the disputed claim language in the '249 patent.

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Attorneys for Plaintiff Glaxo Group Limited

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on June 30 2006, I electronically filed **PLAINTIFF GLAXO GROUP LIMITED'S OPENING CLAIM CONSTRUCTION BRIEF CONSTRUING THE DISPUTED CLAIM TERMS OF GLAXO'S U.S. PATENT NO. 5,068,249** with the Clerk of Court using CM/ECF which will send notification of such filing and we will hand deliver such filing to the following:

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I hereby certify that on June 30, 2006, I have mailed via Federal Express, the document to the following non-registered participants:

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